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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/328,975	06/09/1999	JOHN A. WOLFF	MIRUS009	7574

25032 7590 10/31/2005

MIRUS CORPORATION  
505 SOUTH ROSA RD  
MADISON, WI 53719

EXAMINER
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SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 10/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/328,975

Applicant(s)

WOLFF ET AL.

Examiner

Richard Schnizer, Ph. D

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 14 October 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1,3 and 5-8 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) 6 and 8 is/are allowed.
- 6) ☐ Claim(s) \_\_\_\_\_ is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 09 June 1999 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)             | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                                    |

### **DETAILED ACTION**

An amendment after final rejection was received and entered on 10/14/05.

Finality of the previous Office Action is withdrawn in view of prior art that has come to the Examiner's attention, necessitating a new rejection under 35 USC 103.

### ***Rejections Withdrawn***

The rejections of claims 1, 3, and 5-8 under 35 USC 102(f) are withdrawn in view of Applicant's declaration filed 10/14/05 indicating that the inventions disclosed in the instant application and in U.S. Patent No. 6,881,576, U.S. Patent No. 6,740,643, U.S. Patent No. 6,740,336, U.S. Patent No. 6,818,626, and U.S. Application No. 10/795,679 were, at the time of their invention owned by, or subject to an obligation of assignment to, Mirus Bio Corporation.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 3, 5, and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Degols et al (Nucl. Acids Res. 19(4): 945-948, 1991) in view of Leonetti et al (J. Nat. Cancer Inst. 88(7): 419-429, 1996), taken with the evidence of Wiethoff et al (J. Biol. Chem. 276(35): 32806-32813, 2001).

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Degols taught methods of inhibiting the proliferation of tumor cell in vivo by forming a composition comprising an anti-*c-myc* anti-sense oligonucleotide conjugated to polylysine, and then forming a ternary complex by addition of polyanions such as heparin, carboxymethylcellulose, alginate, and polyglutamate. See abstract; page 946, column 1, first full paragraph, and Fig. 2 at column 2; page 947 column 1, second full paragraph, and Fig. 3; page 947, column 2, second full paragraph. Degols was silent as to the net charge of the ternary complexes.

Evidence that the ternary complexes had a net negative charge is as follows. To form ternary complexes, Degols used polyanions at a concentration of 100 micrograms/ml, and polylysine(PLL)/oligonucleotide conjugates in a range of concentrations from 1-2 micromolar. Each oligonucleotide was modified with a PLL molecule at the 3' ribose, so each conjugate contained one molecule of PLL, molecular weight 14000. See page 945, column 2, last full paragraph through page 946, column 1, line 6. Assuming a residue molecular weight of 128.2 Da for lysine, 14 kDa PLL has a net charge of 109 positive charges per mole at physiological pH. The myc oligonucleotides were 17 nucleotides in length, so assuming 1 negative charge per nucleotide, the net charge of each conjugate was about  $109 - 17 = 92$  positive charges. So, if Degols used the conjugates at 1-2 micromolar, this is equivalent to a concentration of positive charges of about 92-184 micromolar.

Wiethoff taught that heparin contains an average of 2.4 sulfates and 1 carboxylate per repeating disaccharide, and that each disaccharide has a molecular weight of 535 Da. See page 32807, column 1, lines 3-8 of the fourth full paragraph. So,

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if heparin has 3.4 moles of negative charge per every 535 g, then it contains 0.64 micromoles of negative charge per 100 micrograms. To form ternary complexes, Degols used heparin at concentration of 100 micrograms/ml, i.e. 0.64 micromoles/ml, or 640 micromolar. Thus, in forming ternary complexes, Degols added negative charges to positive charges at a ratio of 640 micromoles to 92-184 micromoles. Absent evidence to the contrary, this led to the formation of negatively charged ternary complexes.

Degols did not teach a method of delivering the complexes in vivo.

Leonetti taught a method of delivering anti-*c-myc* anti-sense oligonucleotides to melanoma cells in mice. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the ternary complexes of Degols in the method of Leonetti. One would have been motivated to do so because Degols showed that use of the ternary complexes allowed one to achieve the same anti-proliferative effect with one tenth the amount of oligonucleotide. Compare Figs. 1 and 2 on page 946. Also Degols taught that polyanions inhibit the normal fusion of secondary lysosomes with phagosomes, leading to decreased degradation of endocytosed molecules. See page 948, lines 7-11 of the paragraph bridging columns 1 and 2.

Thus the invention as a whole was prima facie obvious.

### ***Conclusion***

Claims 6 and 8 are allowable.


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Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.



Richard Schnizer, Ph.D.